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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,489	03/01/2004	Serge Carillo	ST94037B	9027

29693 7590 07/10/2009

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EXAMINER
LONG, SCOTT

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
07/10/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/788,489	CARILLO ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/26/2009 and 10/30/2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/405,920.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Petition (filed 1/26/2009) and TC1600 Director's Petition Decision (filed 2/11/2009). As a result of the Petition Decision, the examiner has been directed to withdraw the finality of the Action (filed 4/30/2008) and therefore, the Claim amendments (filed 10/30/2008) are entered.

Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

Claim Status

Claims 1-8 are pending. Claim 1 is amended. Claims 1-8 are under current examination.

Priority

This application claims benefit as DIV of 09/405,920 (filed 09/24/1999 ABN) which is a CON of 08/737,953 (filed 11/27/1996 ABN) which is a 371 of PCT/FR95/00670 (filed 05/22/1995). The application also claims benefit from foreign application, FRANCE FR94/06583 (filed 05/31/1994). The instant application has been granted the benefit date, 31 May 1994, from the application FRANCE FR94/06583.

RESPONSE TO ARGUMENTS

35 USC § 103

The rejection of claims 1-8 under 35 U.S.C. 103(a) as being unpatentable over Henkart et al. (US-5,607,831, issued 4 Mar 1997) in view of Squier et al. (Journal of Cellular Physiology, May 1994; 159(2): 229-237) and further in view of Maki et al. (The Journal of Biological Chemistry, Nov.15, 1989; 264(32): 18866-18869) and further in view of Haake et al. (J Invest Dermatol, 1993; 101: 107-112) is withdrawn in response to the applicants claim amendments.

The amended claims have been fully considered and are persuasive. Claim 1 has been amended to recite "to the cell extract." The cited references do not teach such a limitation. Therefore, the examiner finds the claim amendments persuasive.

Therefore, the examiner hereby withdraws the rejection of claims 1-8 under 35 USC 103(a) as being unpatentable over Henkart et al. in view of Squier et al. and further in view of Maki et al. and further in view of Haake et al.

NEW GROUNDS OF REJECTION

Claim amendments - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramsby et al. (Electrophoresis. Feb 1994; 15(2): 265-277) and further in view of

Robaye et al. (Electrophoresis. 1994; 15: 503-510) and further in view of Squier et al. (Journal of Cellular Physiology, May 1994; 159(2): 229-237) and further in view of Lowe et al. (Nature. 29 April 1993; 362: 847-849). further in view of Lane et al (*British Medical Bulletin*. 1994; 50(3):582-599).

Claim 1 is directed to a method for detecting an inhibitor of p53 protein degradation comprising providing a cell extract containing one or more p53 proteins and one or more proteases, administering a peptide or protein inhibitor of calpain protease activity to the cell extract, and measuring p53 protein and p53 protein fragments.

The instant invention is claimed to be a method for detecting inhibitors of p53 protein degradation. In other words, the claimed method is designed to identify inhibitors of p53 induced apoptosis. However, the method uses an indirect measure of discovering inhibitors of p53 apoptosis, by adding calpain inhibitors to cell extracts and measuring p53 fragmentation. Calpain proteases are known to be involved in apoptosis. Essentially, the method is a method of identifying calpain protease inhibitors, where the particular protein cleaved is p53.

Claim 2 is directed to the method of claim 1, wherein the inhibitor administered is a calpastatin.

Claim 3 is directed to the method of claim 2, wherein the calpastatin is encoded by one of SEQ ID NO: 1-3.

Claim 4 is directed to method of claim 1, wherein the cell extract is derived from a tumor cell.

Claim 6 is a method of claim 4, wherein the inhibitor is a calpastatin.

Claims 5 and 7 are directed to the methods of claims 1 and 4, respectively, wherein the inhibitor is a fragment of calpastatin.

Claim 8 is directed to the method of claim 1, wherein measuring the p53 protein and p53 protein fragments is performed using gel electrophoresis.

Ramsby et al. teach providing a cell extract containing one or more p53 proteins and one or more proteases, administering an inhibitor of calpain protease activity to the cell extract, and measuring p53 protein and p53 protein fragments. Both the claimed invention and the method of Ramsby belong to a larger genus of methods encompassing administration of calpain inhibitors to cell extracts and subsequent detection of p53.

Ramsby et al. teach, "extraction of isolated hepatocytes" in the presence of EDTA (page 268, col.1, Results and Discussion). Ramsby et al. teach EDTA is "an effective inhibitor of the calcium-activated proteases, calpains I and II." (page 271, col.1, 2nd parag.). Ramsby et al. teach, "two-dimensional (2-D) gel electrophoresis… used…to assess…protein… degradation" (page 265, Abstract). Ramsby et al. teach "distribution of proteins in 2-D gels" including p53 protein (page 275). In addition, Rambsy et al. teach calpastatin is an inhibitor of calpain (page 271, col.1, 2nd parag.). Importantly, Rambsy et al. teach the general method of using 2D gel electrophoresis to study the effect of compounds on protein degradation (including p53) from cell extracts. Further, Ramsby teaches that calpastatin is a protein inhibitor of the protease, calpain. Finally, Ramsby teaches that the 2-D gel methodology can be used to detect and monitor enzyme-inhibitor dynamics (page 276, col.2, line 13).

However, Ramsby et al. do not specifically teach administering protein inhibitors of calpain to the cell extract.

Robaye et al. teach "apoptotic cell death analyzed at the molecular level by two-dimensional gel electrophoresis" and "a role for proteolysis in apoptosis is supported by evidence of increased protease activity during apoptotic regression and by the ability of protease inhibitors to block apoptosis in come cases" (page 502, col.2, lines 6-10). Therefore, Robaye et al. teach a similar method as Ramsby, but specifically indicate its utility for analyzing proteolytic cleavage fragments generated during apoptosis. Analyzing proteolytic cleavage fragments generated during apoptosis is a general idea of the claimed method.

However, Robaye et al. do not teach detecting p53 and P53 fragments from among the proteolytic cleavage fragments detected on the 2-D gel. Furthermore, Robaye et al. have not treated the cell extracts with particular proteolysis inhibitors of calpain.

Squire et al provide a method for assaying proteolysis in cell extracts treated with inhibitors of calpain, particularly calpastatin (page 230, Calpain activity assays). The cell extracts were from apoptotic thymocytes induced by low level radiation (abstract). Squier et al. also teach making cell extracts and performing Western blots (including electrophoresis) in order to test samples.

Squier et al. do not teach that p53 is a ligand of calpain. Squier et al. also do not teach that p53 is involved in apoptosis, although this was generally known in the art at the time Squier was published.

Lowe et al. teach "p53 is required for radiation-induced apoptosis in mouse thymocytes" (title).

Lane et al. teach that p53 undergoes proteolysis during apoptosis. Lane further suggests that p53 is degraded by the ubiquitin pathway in cells where DNA damage has occurred (page 592, Regulation of p53 Function).

In addition, the instant specification states, "Calpastatin is a known inhibitor of the calpains. Its sequence has been described in the prior art (SEQ ID No. 1)." (page 5, lines 22-24, emphasis added by examiner).

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to combine the teachings of Ramsby et al. and Robaye et al. and Squier et al. and Lowe et al. in a method for detecting an inhibitor of p53 protein degradation by administering a protein inhibitor of calpain protease.

The person of ordinary skill in the art would have been motivated to combine these references. While none of the above cited references specifically indicate that p53 is a substrate of calpain, both p53 and calpain are shown to be involved in the apoptotic pathway, particularly as is indicated by Squier et al. and Lowe et al. In addition, the cited methods encompass detecting proteolytic cleavage during apoptosis and further analyze inhibitors of such proteolytic cleavage. Additionally, the cited art teaches that that p53 undergoes proteolysis during apoptosis and that calpastatin inhibits proteolytic activity of calpain. Therefore, a skilled artisan would be guided by the cited art to devise a method of detecting proteolytic cleavage of p53 protein, using the protein inhibitor, calpastatin.

Absent evidence to the contrary, an artisan would have expected success, because performing gel electrophoresis on cell extracts is well known.

Therefore the method as taught by Ramsby et al. and Robaye et al. and Squier et al. and Lowe et al. and Lane et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SDL/ Scott Long Patent Examiner, Art Unit 1633	/Janet L. Epps-Smith/ Primary Examiner, Art Unit 1633